

SECTION 1

Bilateral Predominantly Symmetric Abnormalities

Cases

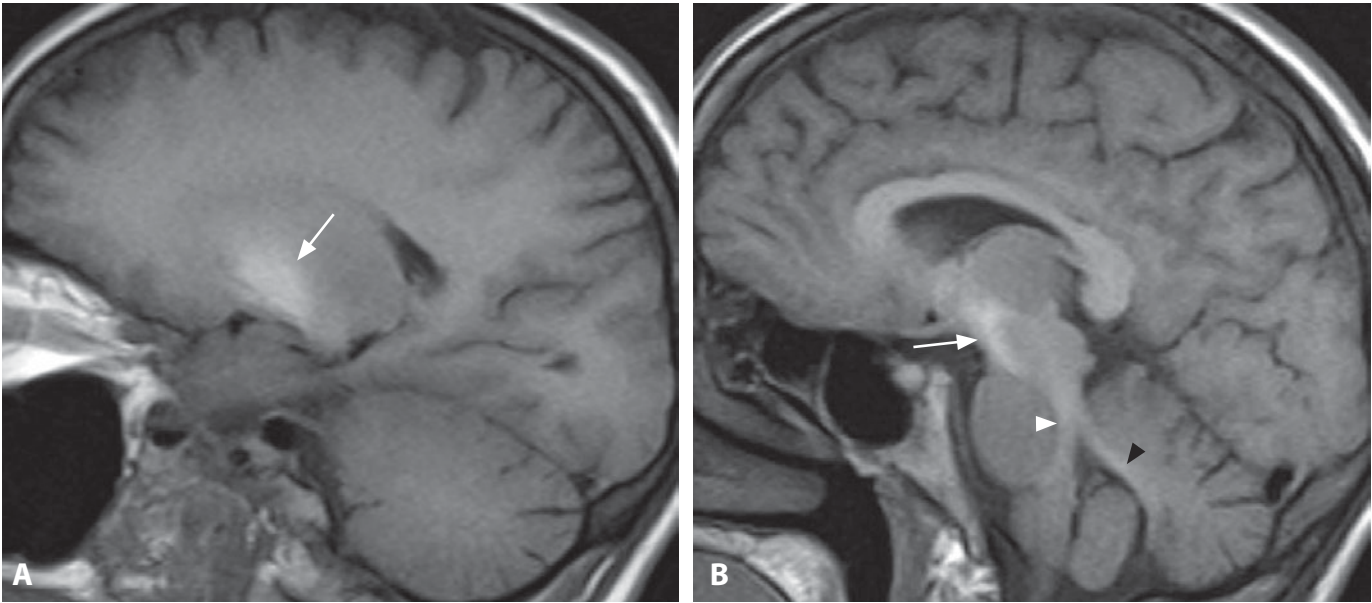
- 1 Hepatic Encephalopathy  
Maria Vittoria Spampinato
- 2 Neurofibromatosis Type 1 – UBOs  
Andrea Rossi
- 3 Carbon Monoxide Intoxication  
Benjamin Huang
- 4 Pantothenate Kinase-Associated Neurodegeneration (Hallervorden–Spatz Syndrome)  
Andrea Rossi
- 5 Methanol Intoxication  
Benjamin Huang
- 6 Wilson Disease  
Benjamin Huang
- 7 Hypoxic Ischemic Encephalopathy in Term Neonates  
Mariasavina Severino
- 8 Cryptococcosis  
Benjamin Huang
- 9 Gangliosidosis GM2  
Mariasavina Severino
- 10 Leigh Disease  
Mariasavina Severino
- 11 Deep Cerebral Vein Thrombosis (DCVT)  
Benjamin Huang
- 12 Creutzfeldt–Jakob Disease (CJD)  
Benjamin Huang
- 13 Global Cerebral Anoxia in Mature Brain  
Maria Vittoria Spampinato and Zoran Rumboldt
- 14 Wernicke Encephalopathy  
Giulio Zuccoli
- 15 Amyotrophic Lateral Sclerosis  
Mauricio Castillo
- 16 Glutaric Aciduria Type 1  
Mariasavina Severino
- 17 Subcortical Band Heterotopia  
Andrea Rossi
- 18 Bilateral Perisylvian Polymicrogyria (BPP)  
Mariasavina Severino
- 19 Lissencephaly  
Mariasavina Severino
- 20 Herpes Simplex Encephalitis  
Mauricio Castillo and Zoran Rumboldt
- 21 Limbic Encephalitis  
Mauricio Castillo
- 22 CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy)  
Zoran Rumboldt
- 23 Megalencephalic Leukoencephalopathy with Subcortical Cysts  
Mariasavina Severino

- 24 Canavan Disease  
Andrea Rossi and Chen Hoffman
- 25 HIV Encephalopathy  
Zoran Rumboldt and Mauricio Castillo
- 26 Radiation- and Chemotherapy-Induced Leukoencephalopathy  
Maria Vittoria Spampinato
- 27 Leukoaraiosis (Microangiopathy)  
Alessandro Cianfoni
- 28 Periventricular Edema in Acute Hydrocephalus  
Alessandro Cianfoni
- 29 Hypoglycemia  
Benjamin Huang
- 30 X-linked Adrenoleukodystrophy (X-ALD)  
Mariasavina Severino
- 31 Periventricular Leukomalacia (PVL)  
Alessandro Cianfoni
- 32 Posterior Reversible Encephalopathy Syndrome (PRES, Hypertensive Encephalopathy)  
Maria Vittoria Spampinato and Zoran Rumboldt
- 33 Alexander Disease  
Mariasavina Severino
- 34 Metachromatic Leukodystrophy  
Andrea Rossi and Zoran Rumboldt
- 35 Neurodegenerative Langerhans Cell Histiocytosis (ND-LCH)  
Zoran Rumboldt and Andrea Rossi
- 36 Remote Cerebellar Hemorrhage  
Maria Gisele Matheus
- 37 Spontaneous Intracranial Hypotension  
Maria Vittoria Spampinato

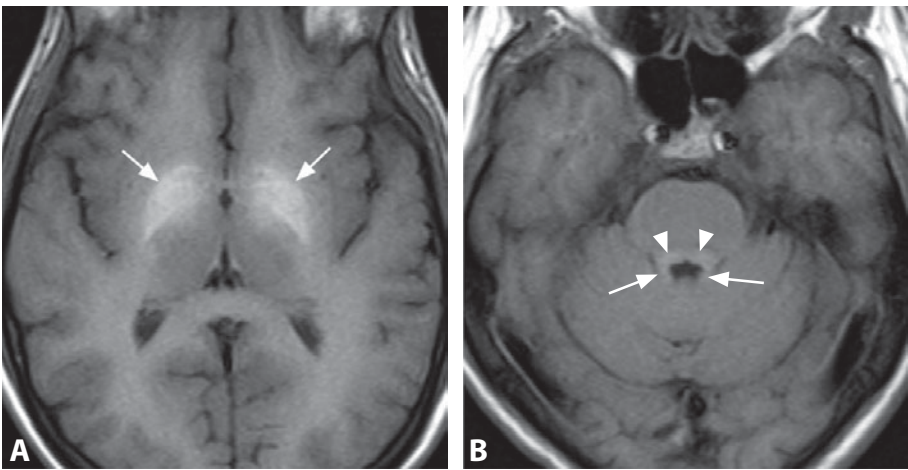
Other Relevant Cases

- 59 Multiple System Atrophy (MSA)  
Zoran Rumboldt and Mauricio Castillo
- 60 Maple Syrup Urine Disease (MSUD)  
Andrea Rossi
- 66 Osmotic Myelinolysis  
Mauricio Castillo
- 87 Benign External Hydrocephalus  
Maria Vittoria Spampinato
- 88 Normal Pressure Hydrocephalus  
Alessandro Cianfoni
- 89 Alzheimer Disease  
Maria Vittoria Spampinato
- 90 Frontotemporal Lobar Dementia  
Maria Vittoria Spampinato
- 91 Huntington Disease  
Zoran Rumboldt and Benjamin Huang
- 184 Congenital Cytomegalovirus Infection  
Zoran Rumboldt and Chen Hoffman

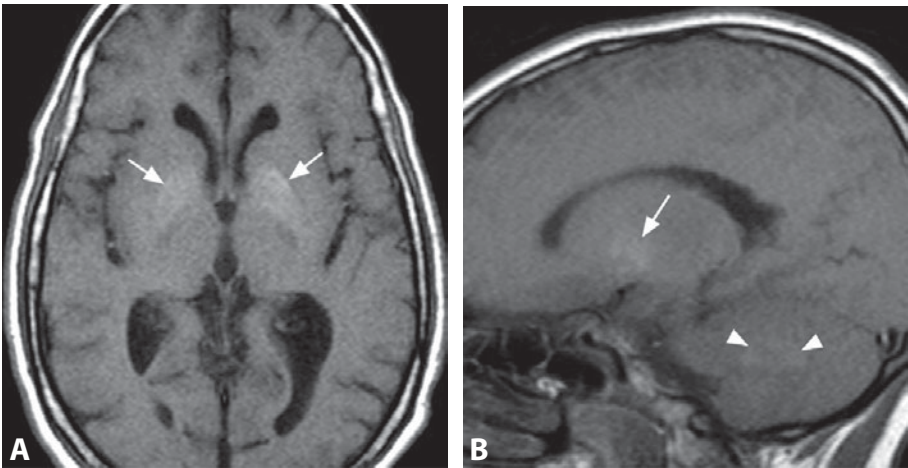
CASE 1 | Hepatic Encephalopathy



**Figure 1.** Sagittal non-contrast T1WI (A) demonstrates hyperintensity of the globus pallidus (arrow). A more medial sagittal T1WI (B) shows increased signal in the substantia nigra (arrow), dorsal brainstem (white arrowhead), and cerebellum (black arrowhead).



**Figure 2.** Axial non-contrast T1WI through the basal ganglia (A) shows bilateral bright globus pallidus (arrows). Axial T1WI image through the pons (B) reveals hyperintensity involving superior cerebellar peduncles (arrows) and tectum (arrowheads).



**Figure 3.** Axial non-contrast T1WI (A) shows a more subtle globus pallidus hyperintensity (arrows). Sagittal T1WI (B) demonstrates high signal in the region of the dentate nucleus (arrowheads) in addition to globus pallidus (arrows).

CASE  
1

# Hepatic Encephalopathy

MARIA VITTORIA SPAMPINATO

## Specific Imaging Findings

Classic brain MR imaging finding in patients with hepatic encephalopathy (HE) is bilateral symmetric globus pallidus hyperintensity on T1-weighted images. When more prominent, high T1 signal is also present in substantia nigra, subthalamic nucleus, tectum, and cerebellar dentate nucleus, with no corresponding findings on T2-weighted images or on CT. Additional MRI findings include diffuse white matter T2 hyperintensity involving predominantly the hemispheric corticospinal tract and focal bright T2 lesions in subcortical hemispheric white matter. MR spectroscopy obtained with short echo time shows depletion of *myo*-inositol. Myo/Cr ratios are decreased not only in cirrhotic patients with clinical or subclinical encephalopathy, but also in individuals without encephalopathy. Increased levels of glutamine/glutamate have also been observed, particularly in severe cases. All these MR imaging findings – bright T1 lesions, white matter T2 hyperintensity, and MRS abnormalities – tend to improve and return to normal with restoration of liver function, such as following a successful liver transplantation. Characteristic MRI appearance of acute hyperammonemic encephalopathy appears to be bilateral symmetric cortical T2 hyperintensity involving the insula and cingulate gyrus, best seen on FLAIR and DWI.

## Pertinent Clinical Information

HE includes a spectrum of neuropsychiatric abnormalities occurring in patients with liver dysfunction. Most cases are associated with cirrhosis and portal hypertension or portal-systemic shunts. It is a reversible metabolic encephalopathy, characterized by personality changes and shortened attention span, anxiety and depression, motor incoordination, and flapping tremor of the hands (asterixis). In severe cases, coma and death may occur. Severe forms of hepatic encephalopathy are usually diagnosed clinically; however, mild cases are sometimes difficult to identify even with neuropsychological testing.

## Differential Diagnosis

### Manganese Intoxication

- indistinguishable T1 hyperintensity (same presumed pathophysiology)

### Long-Term Parenteral Nutrition

- indistinguishable T1 hyperintensity (same presumed pathophysiology)
- abnormalities disappear when manganese is excluded from the solution

### Physiologic Basal Ganglia Calcifications (187)

- typically punctuate to patchy and not diffuse
- calcifications on CT

### Neurofibromatosis Type 1 (2)

- typically patchy, not diffuse
- additional areas of involvement

### Carbon Monoxide Intoxication (3)

- bright T2 signal and reduced diffusion in bilateral globus pallidus

### Hypoxic Ischemic Encephalopathy (7)

- bright T1 signal around the posterior limb of the internal capsule (thalamus, putamen, globus pallidus)
- affects neonates

### Kernicterus

- increased T1 and T2 signal of the globus pallidus
- affects neonates

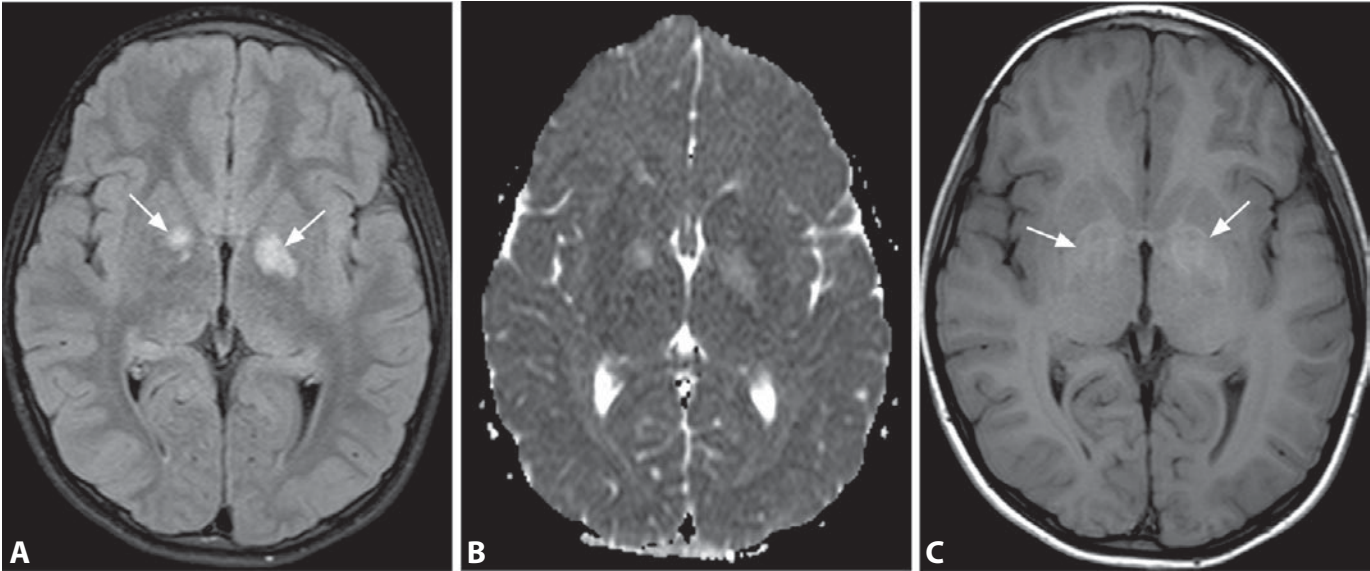
## Background

HE (or portal systemic encephalopathy) is caused by inadequate hepatic removal of nitrogenous compounds or other toxins ingested or formed in the gastrointestinal tract. Failure of the hepatic detoxification systems results from compromised hepatic function as well as extensive shunting of splanchnic blood directly into the systemic circulation by porto-systemic collateral vessels. Factors precipitating hepatic encephalopathy in patients with chronic hepatocellular disease include dietary protein load, constipation, and gastrointestinal hemorrhage. As a result, toxic compounds, such as ammonia, manganese, and mercaptans gain access to the central nervous system. These series of events lead to the development of HE. The neurotoxic effects of ammonia are mediated by its effects on several neurotransmitter systems and on brain energetic metabolism. The T1-weighted MRI findings are considered related to the accumulation of manganese, and its serum concentration in cirrhotic patients is tripled compared to normal individuals. Manganese accumulation may lead to parkinsonism, especially with substantia nigra involvement. White matter T2 hyperintensity is thought to be caused by mild brain edema and focal lesions have been linked to spongy degeneration involving the deep layers of the cerebral cortices and the underlying U-fibers.

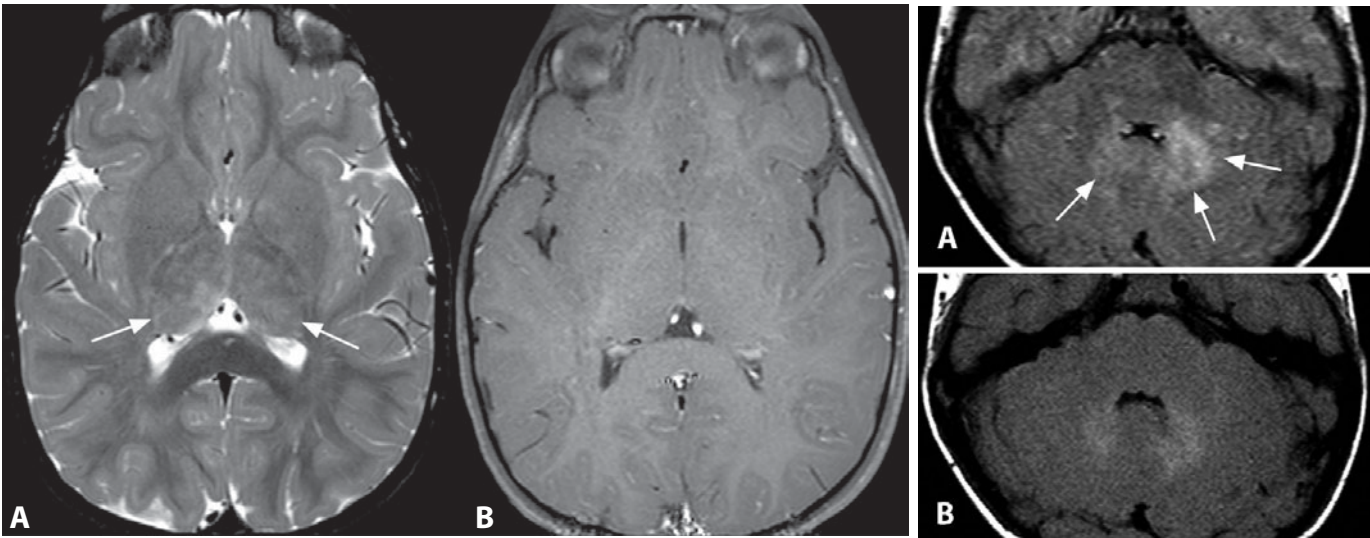
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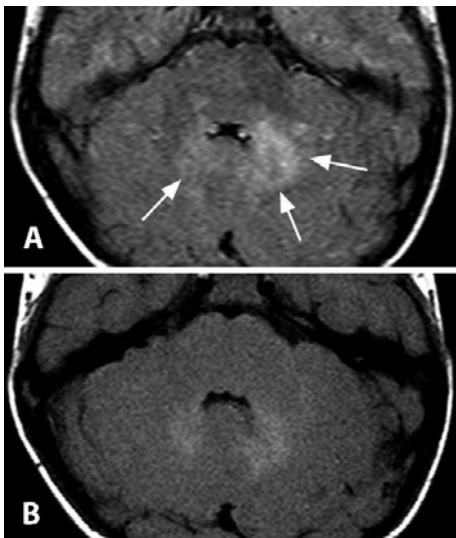
CASE 2 | Neurofibromatosis Type 1 – UBOs



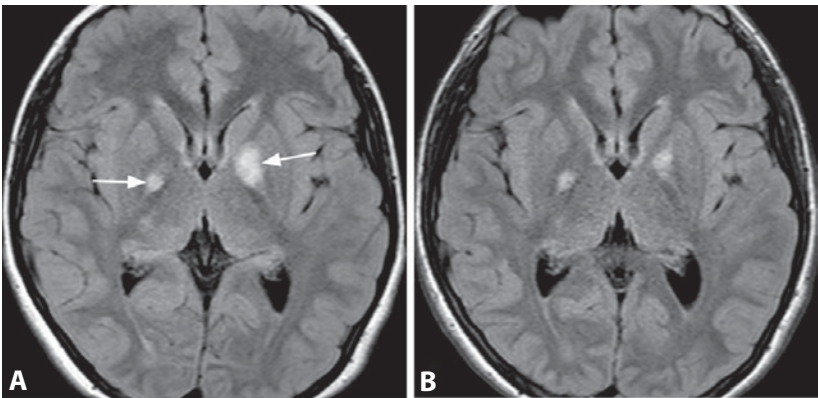
**Figure 1.** Axial FLAIR image (A) shows bilateral bright signal abnormalities (arrows) in the globi pallidi. There is also increased diffusivity on the ADC map (B) and mild hyperintensity (arrows) on T1WI (C).



**Figure 2.** T2WI in another patient (A) depicts multiple hyperintense foci (arrows) predominantly in the thalami without enhancement on post-contrast T1WI (B).



**Figure 3.** Bright foci in medial cerebellum (arrows) are seen on FLAIR (A) and T1WI (B).



**Figure 4.** Axial FLAIR image at the basal ganglia level in a 10-year-old patient (A) shows bilateral patchy hyperintense abnormalities primarily involving the globi pallidi (arrows). FLAIR image acquired 3 years later at the same level (B) reveals spontaneous regression of these lesions.

## Neurofibromatosis Type 1 – UBOs

ANDREA ROSSI

### Specific Imaging Findings

Unidentified bright objects (UBOs) are the most common intracranial lesions in patients with neurofibromatosis type 1 (NF1), occurring in about two-thirds of the patients. They typically appear as hyperintense foci on long repetition time (T2-weighted, FLAIR, PD) MR images and iso- to mildly hypointense on T1-weighted images; sometimes they show slight T1 shortening, which has been related to myelin clumping or microcalcification. Mass effect, vasogenic edema, and contrast enhancement are characteristically absent. These lesions typically appear at around 3 years of age, increase in number and size until 10–12 years, and then tend to spontaneously decrease in size and number, or even completely disappear. They are typically multiple and most commonly involve the white matter and basal ganglia (especially the globi pallidi), usually in a bilateral asymmetric fashion. Other common locations include the middle cerebellar peduncles, cerebellar hemispheres, brainstem, internal capsule, splenium of the corpus callosum, and hippocampi. MRS performed within these lesions may be normal or show slightly decreased NAA and increased choline levels.

### Pertinent Clinical Information

The correlation between the presence and extent of UBOs and the cognitive deficit or learning disability is still controversial. It has been suggested that the anatomic location of neurofibromatosis bright objects (NBOs) is more important than their presence or number. It seems that thalamic NBOs are in particular significantly associated with neuropsychological impairment. A patient with NF1 may present other CNS lesions (optic pathway tumors and other brain and/or spine low-grade gliomas), skin lesions (café-au-lait spots, axillary and inguinal freckling and cutaneous neurofibromas), ocular Lisch nodules and skeletal and skull manifestations (kyphoscoliosis, overgrowth or undergrowth of bone, erosive defects due to neurofibromas, pseudoarthrosis of the tibia and dysplasia of the greater sphenoidal wing).

### Differential Diagnosis

#### *Low-Grade Gliomas in NF1*

- markedly hypointense on T1-weighted images
- mass effect and possible contrast enhancement
- may also spontaneously regress

#### *Kernicterus*

- symmetric bilateral pallidal hyperintensity on T1- and T2-weighted images
- clinical history of neonatal hyperbilirubinemia

#### *PKAN (4)*

- symmetric eye-of-the-tiger sign (central hypointensity within hyperintense globi pallidi)

#### *Methylmalonic Aciduria*

- symmetric diffuse bilateral pallidal T2 hyperintensity

#### *Hemolytic–Uremic Syndrome*

- patients are acutely symptomatic, characteristically with diarrhea and renal failure
- generally symmetric T2 hyperintensity, primarily of the basal ganglia and thalami
- areas of T1 hyperintensity are frequently present, reflecting hemorrhage

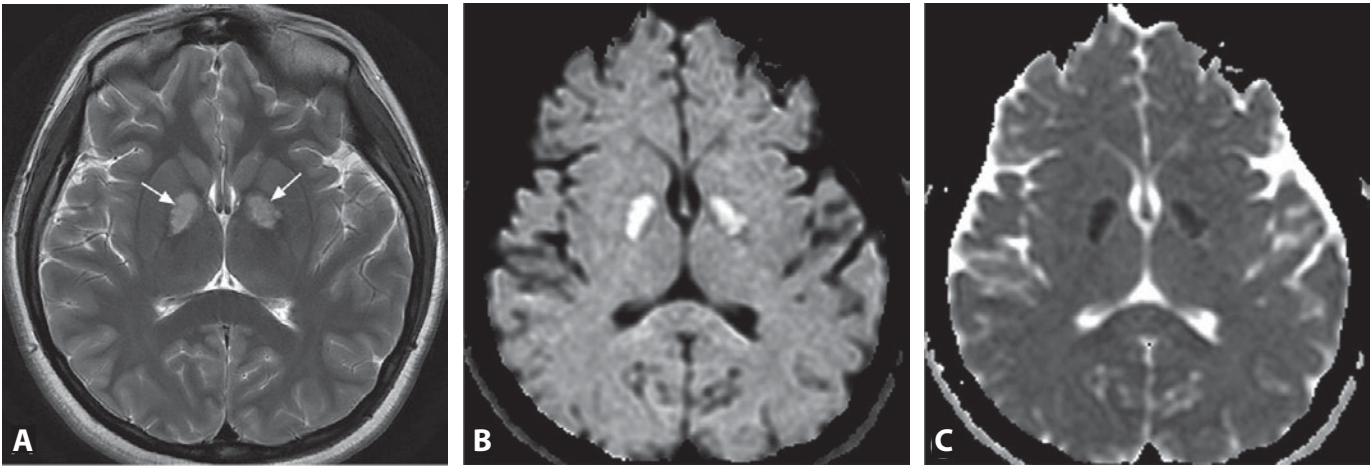
### Background

UBOs have been described in 60–80% of NF1 cases, but the incidence rises to 90% in patients with concurrent optic glioma. These abnormalities have received numerous designations, among which are “histogenetic foci”, focal areas of signal intensity (FASI), non-specific bright foci, and “neurofibromatosis bright objects” (NBOs). The exact nature and significance of UBOs are still unknown. Although they have been related to dysplastic glial proliferation, hamartomatous changes, or heterotopia, no histological evidence has been found to support these hypotheses. Pathological studies, performed in three cases by DiPaolo *et al.*, showed spongiform myelinopathy or vacuolar changes of myelin without frank demyelination, thereby supporting abnormal myelination as a causal factor. Although UBOs are traditionally considered to be transient and benign, proliferative changes (development of tumors from previously recognized UBOs) have been described in children with larger than usual number and volume of NBOs.

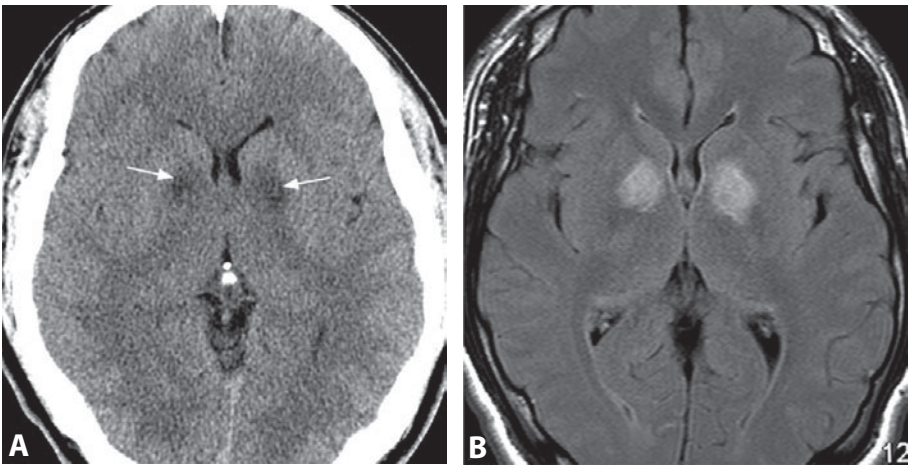
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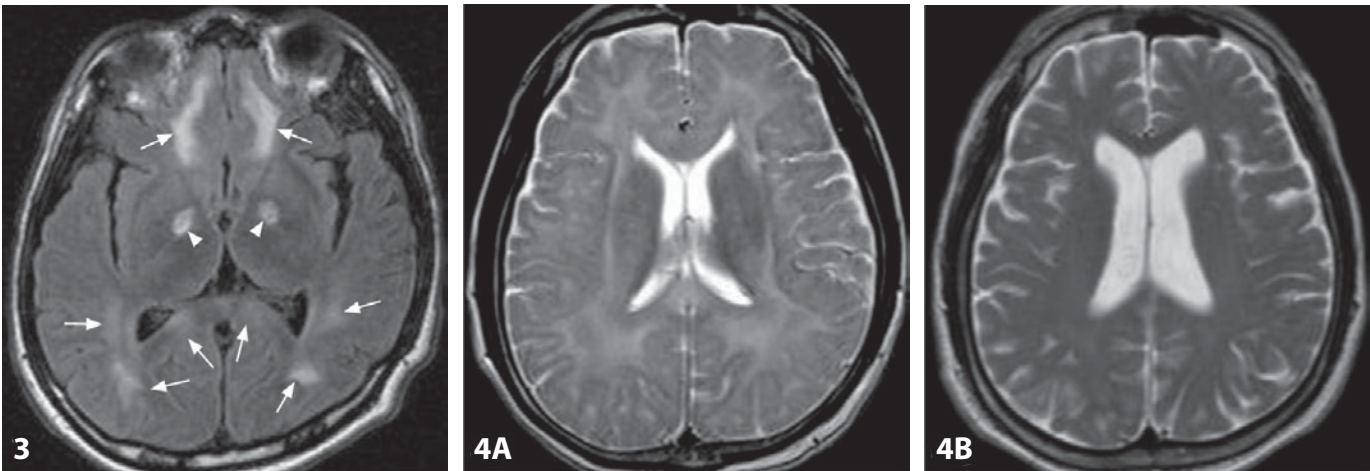
CASE 3 | Carbon Monoxide Intoxication



**Figure 1.** Axial T2WI (A) demonstrates symmetric hyperintense lesions (arrows) in the globi pallidi. Corresponding DWI image (B) shows bright signal of the lesions, which becomes dark on ADC map (C), consistent with reduced diffusivity.



**Figure 2.** Axial non-enhanced CT image (A) shows symmetric hypodensities (arrows) that are centered at bilateral globus pallidus. Corresponding FLAIR image (B) reveals the characteristic bilateral abnormal bright signal in the globi pallidi, typical for the acute phase of the abnormality. Courtesy of Chung-Ping Lo.



**Figure 3.** Axial FLAIR image 10 days after intoxication shows new bilateral white matter hyperintensities (arrows), in addition to the initial globi pallidi lesions (arrowheads).

**Figure 4.** Axial T2WI 1 month later (A) demonstrates diffuse white matter hyperintensity. Corresponding T2WI 19 months later (B) reveals resolution of signal abnormality and progressive brain atrophy. Courtesy of Chung-Ping Lo.

## Carbon Monoxide Intoxication

BENJAMIN HUANG

### Specific Imaging Findings

The globus pallidus is the most common and characteristic site of brain involvement in acute carbon monoxide (CO) poisoning and CT usually shows symmetric hypodensity. On MRI, the pallidi demonstrate low T1 and high T2 signal with reduced diffusion. T1 hyperintensity and a rim of low T2 signal are sometimes seen, reflecting hemorrhagic necrosis. Patchy or peripheral contrast enhancement may occur in the acute phase. Similar MRI findings are occasionally seen in the substantia nigra, hippocampus and cerebral cortex. In patients who develop a delayed leukoencephalopathy, bilateral symmetric confluent areas of high T2 signal are found in the periventricular white matter and centrum semiovale, along with mildly reduced diffusion. Diffuse white matter involvement may also be present.

### Pertinent Clinical Information

Symptoms of mild CO poisoning can include headache, nausea, vomiting, myalgia, dizziness, or neuropsychological impairment. Severe exposures result in confusion, ataxia, seizures, loss of consciousness, or death. Long-term low-level CO poisoning may cause chronic fatigue, affective conditions, memory deficits, sleep disturbances, vertigo, neuropathy, paresthesias, abdominal pain, and diarrhea. On physical examination, patients may demonstrate cherry red lips and mucosa, cyanosis, or retinal hemorrhages. Suspected CO poisoning can be confirmed with blood carboxyhemoglobin levels. Delayed encephalopathy associated with CO toxicity typically occurs 2–3 weeks after recovery from the acute stage of poisoning and is characterized by recurrence of neurologic or psychiatric symptoms. Characteristic symptoms include mental deterioration, urinary incontinence, and gait disturbances. The course of the delayed encephalopathy varies with the severity of intoxication, and symptoms may resolve completely or progress to coma or death.

### Differential Diagnosis

#### Cyanide Intoxication

- may be indistinguishable

#### PKAN (4)

- symmetric eye-of-the-tiger sign (central hypointensity within hyperintense globi pallidi)

#### Global Cerebral Anoxia in Mature Brain (13)

- unlikely to preferentially involve globus pallidus
- bilateral deep gray matter and perirolandic cortex involvement

#### Methanol Intoxication (5)

- characteristic putaminal necrosis
- caudate nucleus may be involved, globus pallidus is typically spared

#### Leigh Disease (10)

- bilateral brainstem, basal ganglia, and cerebral white matter lesions
- basal ganglia involvement is predominantly in the putamina

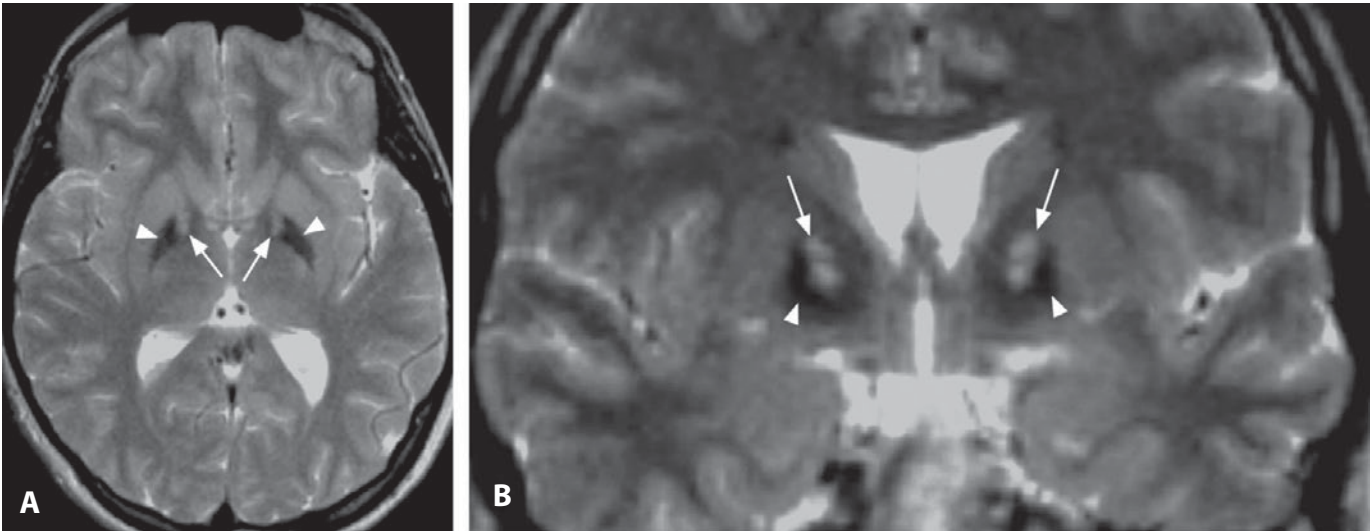
### Background

CO poisoning is the most frequent cause of accidental poisoning in the US and Europe. Common sources of CO, a by-product of incomplete combustion of carbon-based fuels, include faulty furnaces, inadequately ventilated heating sources, and engine exhaust. CO binds avidly to iron in the hemoglobin molecule, with the affinity 250 times higher than that of oxygen, and forms carboxyhemoglobin. This results in reduction of the oxygen-carrying blood capacity of the subsequent tissue hypoxia. Equally important are the direct cellular effects of CO, primarily inhibition of mitochondrial electron transport enzymes by attaching to their heme-containing proteins. Selective vulnerability of the globus pallidus may be related to its high iron content, as carbon monoxide binds directly to heme iron. Decreased cerebral perfusion from an associated cardiovascular insult contributes to the defect in oxygen transport, and the pathological findings of demyelination, edema, and hemorrhagic necrosis are similar to those of other hypoxic–ischemic lesions. Delayed white matter injury may be the result of polymorphonuclear leukocyte activation, which causes brain lipid peroxidation and myelin breakdown. Low fractional anisotropy (FA) values correlate with damage to the white matter fibers in the subacute phase after CO intoxication in patients with persistent or delayed encephalopathy. Administration of 100% normobaric or hyperbaric oxygen is the mainstay of treatment for acute CO poisoning and may improve long-term neurologic sequelae.

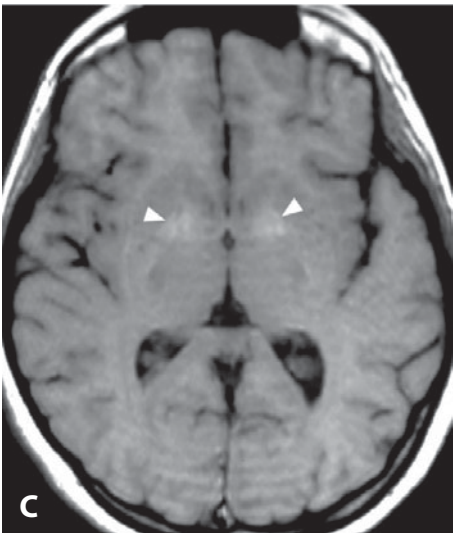
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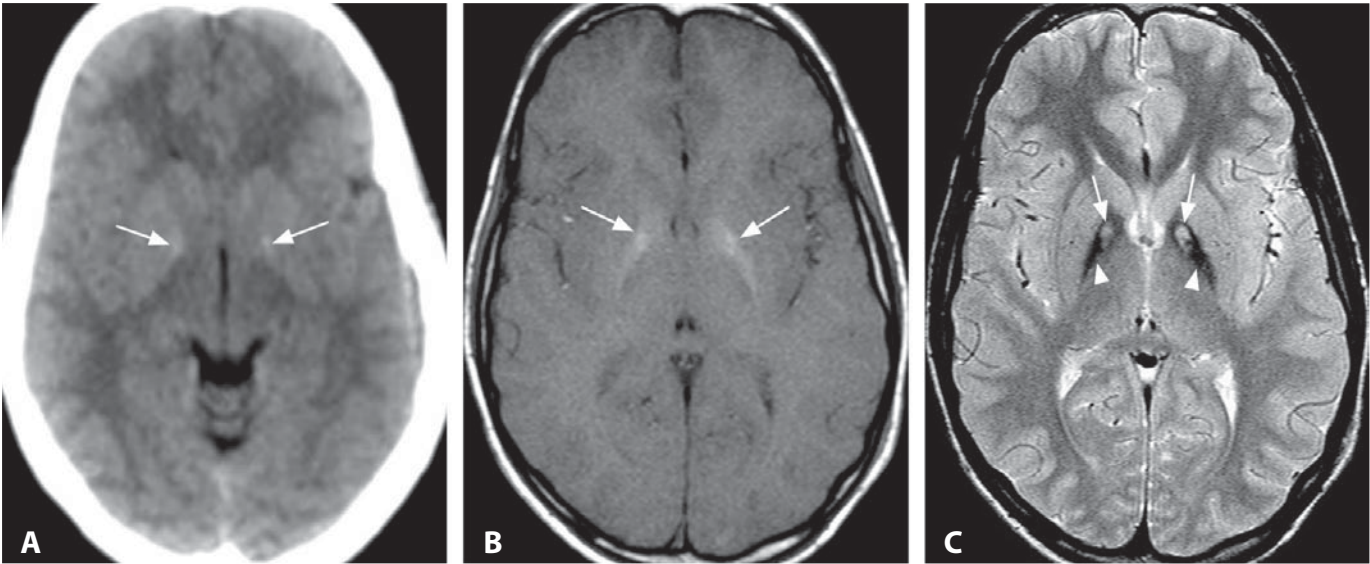
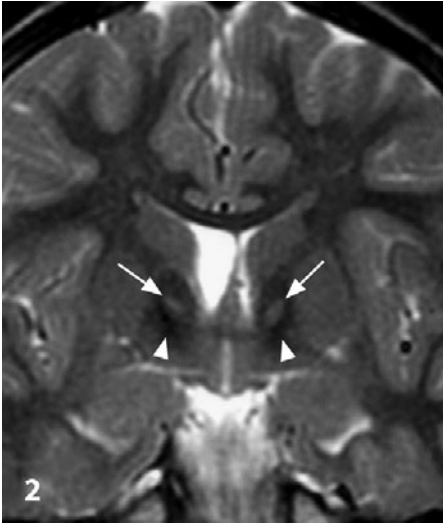
CASE 4 | Pantothenate Kinase-Associated Neurodegeneration (Hallervorden–Spatz Syndrome)



**Figure 1.** Axial (A) and coronal (B) T2WIs show symmetrically hypointense bilateral globus pallidus (arrowheads) with an anteromedial hyperintense area (arrows) resulting in the eye-of-the-tiger sign. T1WI (C) shows faint hyperintense pallidi (arrowheads).



**Figure 2.** Coronal T2WI in another patient reveals hypointense bilateral pallidi (arrowheads) with internal hyperintensity (arrows).



**Figure 3.** Axial non-enhanced CT image (A) shows a subtle anteromedial hyperintensity in bilateral globus pallidus (arrows). Axial T1WI at a similar level shows hyperintensity of the pallidi (arrows), slightly more prominent in the anteromedial aspect. Corresponding T2WI (C) reveals symmetrical bilateral hypointensity of the globus pallidus (arrowheads) containing a focal anteromedial hyperintense area (arrows).

CASE 4

Pantothenate Kinase-Associated Neurodegeneration (Hallervorden–Spatz Syndrome)

ANDREA ROSSI

Specific Imaging Findings

In pantothenate kinase-associated neurodegeneration (PKAN, formerly known as Hallervorden–Spatz syndrome), MRI shows markedly hypointense globi pallidi on T2-weighted images, with a small hyperintense central or anteromedial area. This finding has been labelled the “eye-of-the-tiger” sign and is highly characteristic of PKAN; it is visible on both axial and coronal images. Gradient-echo T2\*-weighted images show more profound hypointensity owing to paramagnetic effects. T1-weighted images may show a corresponding high signal intensity of the pallida. There is no contrast enhancement. CT may reveal symmetrically increased attenuation, primarily in the anteromedial globus pallidus.

Pertinent Clinical Information

This rare autosomal recessive disorder is a part of a group of diseases called “neurodegeneration with brain iron accumulation” (NBIA) which also includes aceruloplasminemia and neuroferritinopathy. PKAN typically presents in older children or adolescents with oromandibular dystonia, mental deterioration, pyramidal signs, and retinal degeneration. Most patients die within 10 years of the clinical onset, although longer survival into early adulthood is possible.

Differential Diagnosis

*HARP Syndrome (hypopre-β-lipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration)*

- may be indistinguishable

*Other Forms of NBIA*

- “eye-of-the-tiger” sign absent

*Toxic Encephalopathies (CO poisoning) (3)*

- globus pallidus T2 hyperintensity without hypointense portion

*Kernicterus*

- globus pallidus T2 hyperintensity without hypointense portion

*Methylmalonic Acidemia*

- globus pallidus T2 hyperintensity without hypointense portion

Normal Iron Deposition

- iron starts accumulating in the pallidi during later childhood and adolescence and is usually seen on MRI from approximately 25 years of age onwards

Background

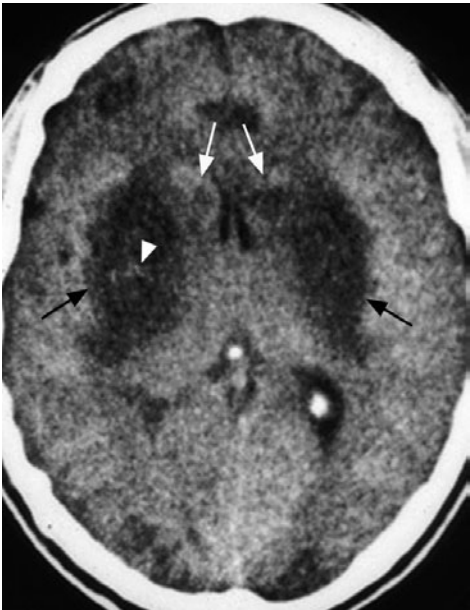
The causal gene, PKAN, is located on the short arm of chromosome 20 and encodes for pantothenate kinase, which regulates the synthesis of coenzyme A from pantothenate, thus participating in fatty acid synthesis and energy metabolism. Defective membrane biosynthesis may result in cysteine increase, which is believed to play a role in the accumulation of iron in the basal ganglia, in turn generating the typical MRI appearance of PKAN. PANK2 mutation analysis confirms the diagnosis, and may be used for prenatal diagnosis in affected families.

Axonal dystrophy with spheroid bodies is found exclusively in the brain, while skin or conjunctival biopsy is typically negative. Abnormal increase of iron deposits within the globus pallidus, with rusty brown discoloration and neuroaxonal swelling, is found on histology. Iron deposits occur either around vessels or as free tissue accumulations and may also involve the substantia nigra and red nuclei. There are associated dystrophic axons and reactive astrocytes in a similar distribution.

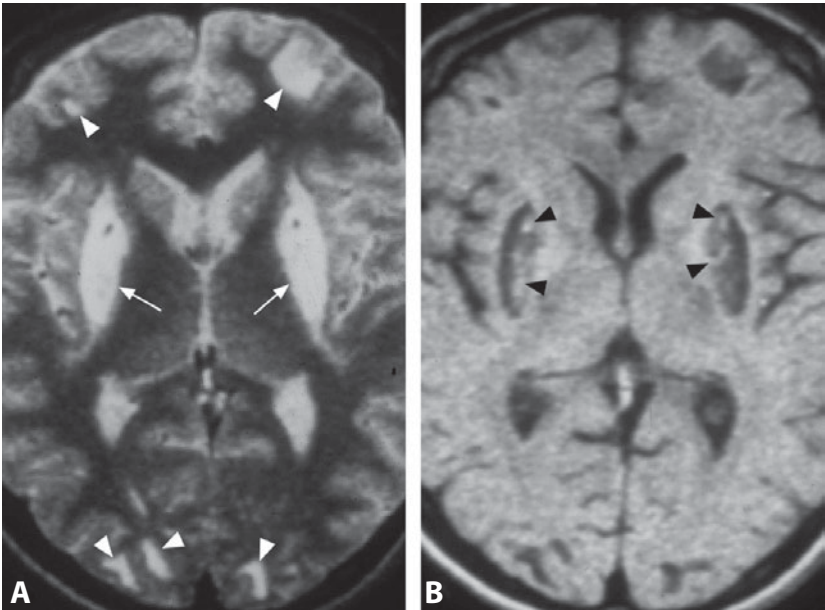
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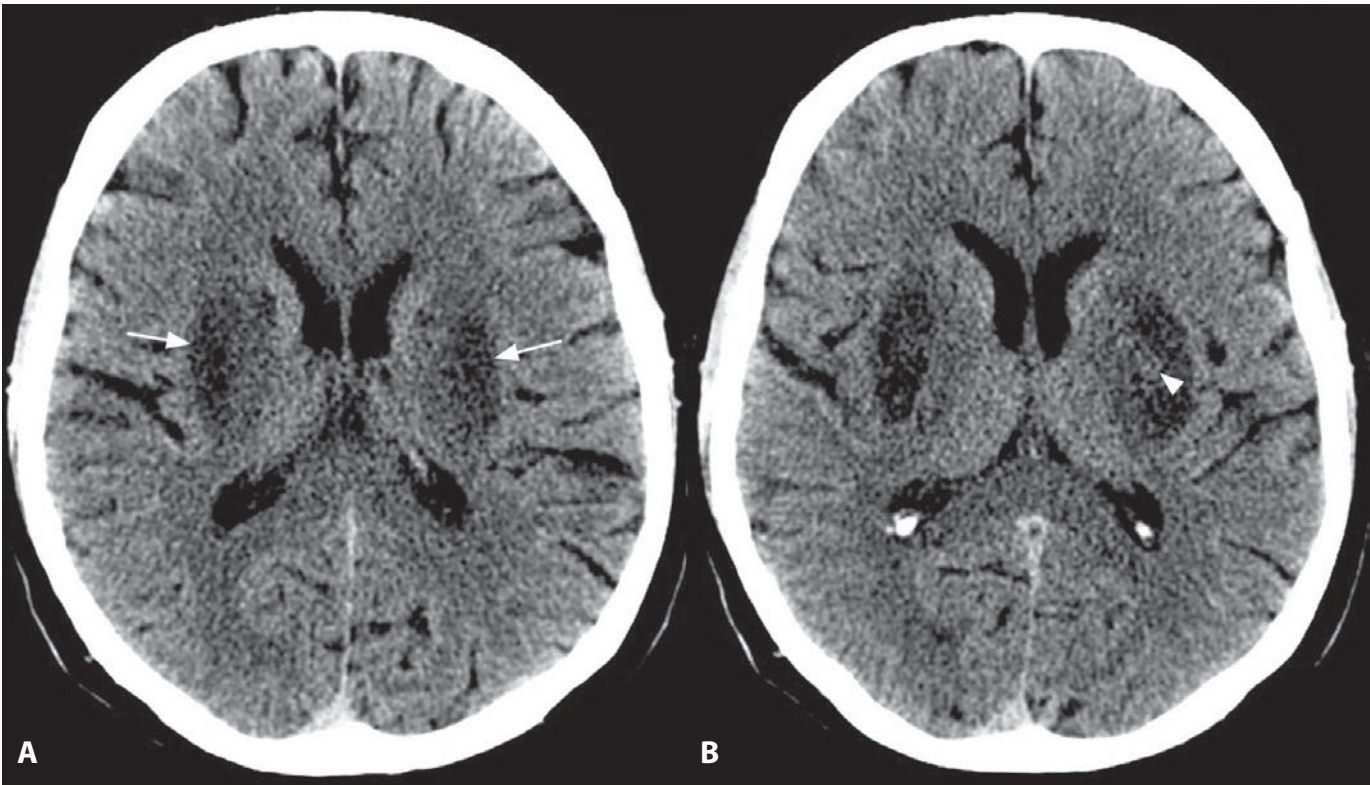
CASE 5 | Methanol Intoxication



**Figure 1.** Axial CT image without contrast demonstrates symmetric basal ganglia swelling and hypodensity (arrows). Small hyperdense foci on the right (arrowhead) are consistent with hemorrhage.



**Figure 2.** Axial T2WI (A) shows symmetric high signal intensity in bilateral putamina (arrows), as well as in subcortical white matter of the left frontal and bilateral occipital lobes (arrowheads). Corresponding T1WI (B) demonstrates predominantly low signal intensity in these regions with a few small foci of higher signal (arrowheads) in the putamina, compatible with small hemorrhages.



**Figure 3.** Axial CT images without contrast (A and B) show symmetric bilateral basal ganglia hypodensity (arrows) predominantly involving putamina. Subtle hyperdensity (arrowhead) within the lesions is consistent with hemorrhage. Courtesy of Pranshu Sharma.